

EDITORIAL COMMENT†

SYNERGIC THEORY OF ANAPHYLAXIS

According to data recently reported by Kellaway and Trethewie,¹ of the Institute for Medical Research, Melbourne, Australia, there are two independent reacting mechanisms in acute anaphylaxis: (a) an explosive formation or liberation of histamine or histamine-like substances by the tissue proteins, followed by (b) the liberation of a second ergin or toxic factor derived from the tissue lipids.

Discovery of this hitherto unsuspected lipoidal anaphylatoxin was a by-product of researches on the pharmacodynamics of certain snake venoms. It has long been known² that in cobra-venom hemolysis, for example, laking of the red blood cells is not due to a direct action of the venom, but to its immediate action on lecithin. The lipolytic enzymes of the venom lead to the formation of a lecithin split-product ("lysocithin") which is directly hemolytic. This active hemolysin can be readily produced by the action of cobra venom on egg yolk or other lecithin containing materials *in vitro*. Chemically the "lysocithin" is a lecithin molecule robbed of one of its oleic acid radicles. The Australian investigators found that in a similar way contraction of smooth muscles under the influence of certain snake venoms is also due to the formation of certain smooth-muscle stimulating split-product of tissue lipids. This active split product or lipoergin can also be produced *in vitro* by the action of venom on egg yolk. The substance is soluble in acetone, by means of which it can be separated from "lysocithin."

The smooth-muscle contracting properties of this lipo-ergin are quite different from those of histamine. Tested on the isolated guinea-pig jejunum, for example, histamine produces an immediate maximum contraction with relatively prompt recovery. The lipo-ergin, in contrast, causes a slowly developing contraction only after a fairly long latent period, with a very sluggish recovery. For this reason the Australian biochemists refer to the lipo-ergin as a "slow-reacting smooth-muscle-stimulating substance" or "SRS."

Histamine and lipo-ergin apparently act on different elements in the smooth muscle. This is shown by a selective suppression of one reactivity by certain therapeutic agents. Exposure to B. welchii toxin, for example, will almost completely desensitize a smooth muscle to the lipo-ergin, without appreciably reducing its histamine sensitivity. Poisoning with relatively large doses of histamine may cause certain

smooth muscles to react to further doses by relaxation, whereas its lipo-ergin sensitivity is practically unaltered. Applying these and other selective depressants, Kellaway and Trethewie found that the typical anaphylactic response of smooth muscle can be analyzed into two components. First there is an initial histamine-like response. In this there is afterwards superimposed a typical slow lipo-ergic tetanus. Therapeutic blockade of both histamine and lipo-ergic sensitivity will prevent anaphylactic smooth muscle contractions, though suppression of either one of these is ineffective.

About ten years ago it was shown by Bartosch³ that if sensitized guinea pig lungs are perfused with Tyrode's solution plus homologous antigen, the hypersensitive tissues liberate histamine into the perfusion fluid. The Australian investigators found that this liberation is mainly confined to the initial stages of the perfusion. Thus in one of their tests, the first two 5 c.c. samples of the perfusion fluid contained a total of about 2.5 gamma histamine. There was a fairly large trace of histamine in the third sample, after which the samples became histamine-free. Analysis of the same samples showed no lipo-ergin in the first sample. Moderate amounts appeared in the second and third samples, with gradually diminishing amounts in subsequent samples.

The evidence, therefore, seems complete that there are two superimposed pathologic internal secretions in acute anaphylactic shock, both of which must be taken into account in any logical attempt at anti-anaphylactic therapy. The Australian physiologists believe that it is reasonable to assume that the same or a similar toxic lipoidal split-product may play an important rôle in other shock-like conditions, particularly in traumatic shock and superficial burns.

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REFERENCES

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2. Manwaring, W. H.: Ztschr. f. Immunitätsforsch. u. exper. Therap., 6, 513, 1910.
3. Bartosch, R., Feldberg, W., and Nagel, E.: Pflügers Arch., 230, 129, 674, 1932.

MALPRACTICE INSURANCE*

At one time or another, during the last thirty years, a considerable number of insurance companies have engaged in writing physicians' professional liability insurance in California. That the business has not generally been profitable is evidenced by the fact that most of these companies no longer offer this coverage. The high incidence of malpractice claims and suits explains why this business is regarded as undesirable, even though the cost to the insured has increased

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* Fourth of a series of articles on Malpractice Prophylaxis (Article I, in July issue, on page 7; Article II, in August, on page 121; Article III, in September, on page 173.)